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Anti-anginal, electrophysiologic and hemodynamic effects of combined beta-blocker/calcium antagonist therapy

G. L. J. VANHALEWEYK, P. W. SERRUYS AND P. G. HUGENHOLTZ

Thoraxcenter, University Hospital Dijkzigt, Erasmus University, Rotterdam, The Netherlands

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Nitrates and beta-blockers have been the mainstay in the therapy of chronic stable angina pectoris for many years. Since an important number of patients remains symptomatic, new potent anti-ischemic agents like the calcium antagonists fulfil a great clinical need. Combined therapy with beta-blockers and calcium antagonists is attractive, since both classes of drugs have differing and eventually complementary modes of action. On the other hand, both have direct negative inotropic and chronotropic effects.

We reviewed the anti-anginal, electrophysiologic and hemodynamic effects of combined treatment with a beta-blocker and verapamil or nifedipine. Combined therapy provides greater symptomatic relief than monotherapy with beta-blockers or slow channel blockers alone. While incidental adverse negative inotropic and chronotropic interactions have been reported, particularly when verapamil is involved, their hemodynamic interplay appears beneficial rather than detrimental in the majority of patients. Indeed, combined therapy is effective and safe, at least when a preserved or only moderately impaired left ventricular function is present. However, caution must be exercised in patients with more impaired left ventricular function, and combined therapy with verapamil must be avoided when conduction disturbances are likely to occur.

Beta-blocking drugs have become widely accepted for treatment of patients with stable angina pectoris[2,3]. They reduce myocardial oxygen requirements, as reflected by a reduction in heart rate and systolic blood pressure at rest and during exercise. However, even when combined with nitrates, an important number of patients fail to respond to these drugs. The availability of a newer class of drugs, the calcium antagonists, may prove to be a significant therapeutic advance in the treatment of such patients. While their mechanisms of action in patients with stable angina pectoris are at present not fully elucidated, reductions in peripheral and coronary vascular resistance are important contributing factors[4]. Furthermore, calcium antagonists, as well as beta-blocking agents, may have direct cardioprotective effects on subcellular systems[5]. The differing, and perhaps complementary actions of both classes of drugs, would make it seem advisable to combine them in the clinical treatment of stable angina pectoris and other ischemic states of the myocardium. Besides, in an as yet undefined number of patients, coronary artery spasm or increases in coronary artery vasomotor tone, may provoke anginal complaints. Beta-blockers may induce unwanted increases in peripheral and coronary vascular tone, which could be counterbalanced by concomitantly administered calcium antagonists[6].

While the beneficial interaction of both classes of drug has indeed been demonstrated[7–17], detrimental responses to combined drug therapy in patients with impaired left ventricular function and/or endstage cardiac disease have also been reported[18–26]. These untoward effects can be explained by the additive negative inotropic and, when verapamil is used as the calcium antagonist, negative chronotropic effects of combined therapy in a subset of patients with severe cardiac disease. For these reasons, we review the anti-anginal, electrophysiologic and hemodynamic effects of combined therapy with beta-blocking agents and verapamil or nifedipine.

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Anti-anginal effects of combined beta-blocker/calcium antagonist therapy

VERAPAMIL AND BETA-BLOCKADE

Subramanian *et al.*[7] compared the efficacy of verapamil (360 mg daily), propranolol (240 mg daily) and combination therapy with the same dose of verapamil and a lower dose of propranolol (120 mg daily) in 14 patients who did not respond completely to either drug when given alone. The mean exercise time for these patients with severely limited exercise tolerance on placebo was $4{\cdot}8 \pm 0{\cdot}2$ min and this increased to $6{\cdot}8 \pm 0{\cdot}6$ min with propranolol and $8{\cdot}0 \pm 0{\cdot}5$ min with verapamil. A further increase to $10{\cdot}1 \pm 0{\cdot}9$ min was observed with the combination of both drugs and seven patients became symptom-free. The double product of systolic blood pressure and heart rate at the same level of exercise achieved with placebo, decreased by 14%. There was a significant reduction in the number of episodes and the maximal depth of ST segment depression, as recorded with 24 h ambulatory monitoring, with combination therapy. Also Leon *et al.*[8] determined the effectiveness of combined verapamil-propranolol in 11 patients, who were not adequately controlled by beta-blockers and nitrates alone. Compared with placebo, verapamil (480 mg daily) improved exercise time in all patients and was more effective than propranolol alone (160 to 320 mg day^{-1}). Verapamil plus propranolol further increased exercise time and nine of 11 patients were angina-free during exercise, while only two of 11 and one of 11 became angina-free with propranolol and verapamil alone respectively. The changes in heart rate, mean blood pressure, pressure-rate product and exercise duration, are presented in Fig. 1. Therapy with propranolol and verapamil resulted in further decreases in mean blood pressure, heart rate and pressure-rate product. In 32 patients with severe angina prectoris not responding to either verapamil or beta-blockers alone, and requiring large dosages of nitroglycerin, Lessem[9] studied the anti-anginal effect of combination therapy. Whereas unfortunately no exercise data are given, more than half of these very symptomatic patients reported marked decreases in nitroglycerin consumption of 50% or more when on combined therapy as compared to single drug therapy.

All three of the studies discussed demonstrate that combined beta-blocker/verapamil treatment can add a new dimension to the treatment of patients with severe chronic anginal complaints.

NIFEDIPINE AND BETA-BLOCKADE

The anti-anginal beneficial effect of combined nifedipine/beta-blocker therapy has been more extensively studied. Fox *et al.*[10] studied 52 patients with incapacitating angina pectoris. Of these 52 patients, 16 were pain free and did not develop ST-T

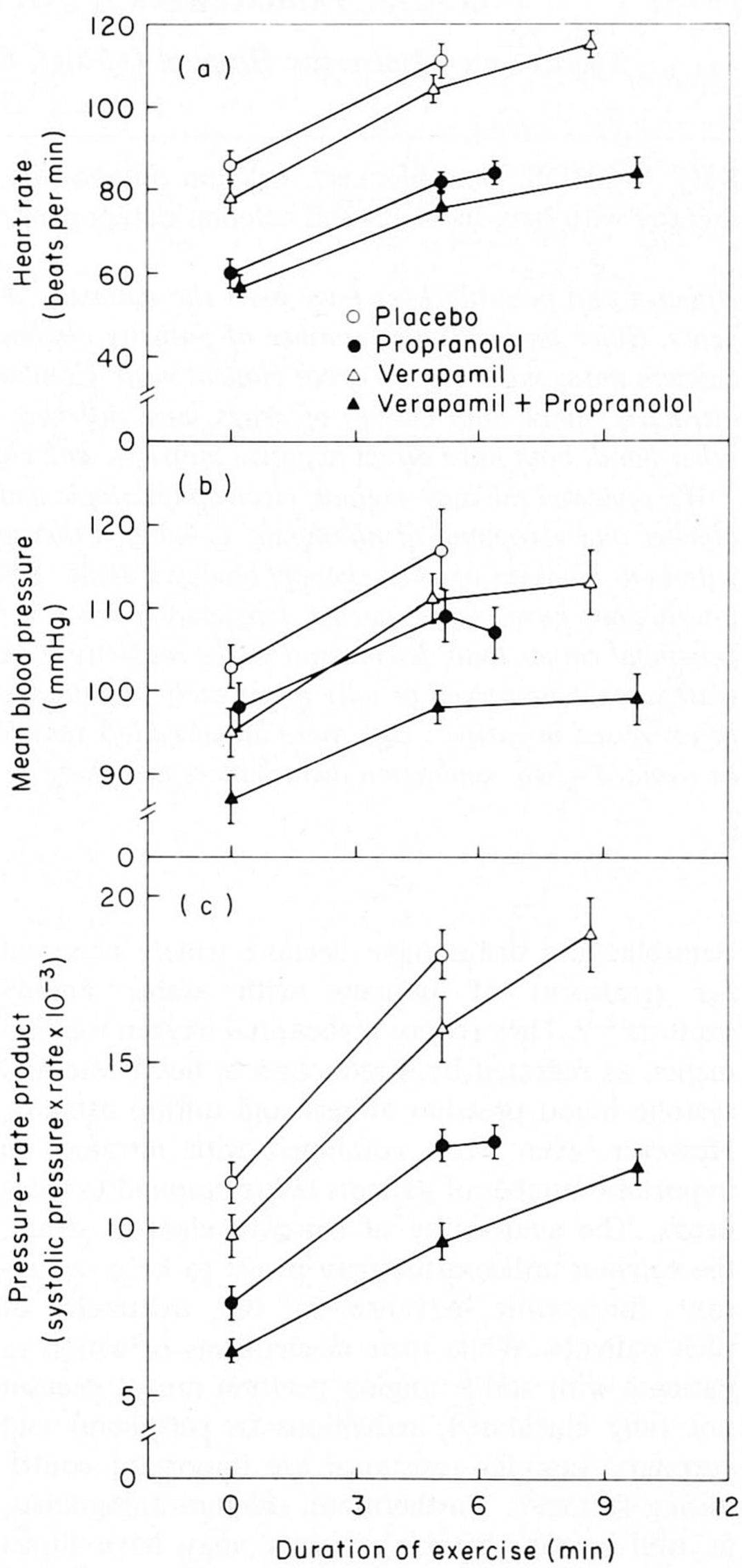

Figure 1 Changes in heart rate, mean blood pressure, pressure-rate product and exercise duration in 11 patients with chronic stable angina on placebo, verapamil, propranolol and combined verapamil-propranolol treatment (Leon *et al.*[8]). Reproduced with permission.

segment changes with increasing doses of propranolol alone. Of the remaining 36 patients the precordial area and severity of exercise-induced ST-T segment depression, as determined by precordial contour mapping, was unchanged in 6 patients, improved in 10 patients and abolished in 14 patients (all of whom were free from chest pain) following combined treatment (propranolol: 300 mg day^{-1}; nifedipine: 50 mg day^{-1}).

Similar additive anti-anginal actions of oral nifedipine in patients receiving propranolol have been demonstrated by other authors[11–17]. The frequency of anginal complaints and of nitroglycerine consumption are further reduced and exercise duration further increased by combined therapy than by either drug alone. Furthermore, the total number of episodes of ST depression detected on ambulatory monitoring is reduced[11,12]. Besides, a more pronounced anti-anginal effect seems possible when combining nifedipine with low doses of propranolol, than with higher doses of propranolol alone[13,17]. The beneficial effects of adding nifedipine to propranolol on exercise-induced ischemia are not always followed by changes in rate-pressure product at maximal exercise or at the same work load as that achieved during placebo. Therefore, mechanisms other than reduction in myocardial oxygen demand may be responsible for the observed improvement[11,17].

Daly *et al.*[15] performed an atrial pacing stress test in 10 patients with chronic stable angina pectoris receiving different beta-blocking therapy, before and after adding 20 mg nifedipine sublingually. Nifedipine prolonged pacing time to angina. At rest, coronary vascular and peripheral resistance decreased and coronary sinus blood flow increased after nifedipine. During atrial pacing, nifedipine caused further decreases in coronary and total peripheral resistances. However, it did not cause a further increase in coronary sinus blood flow. The lactate extraction ratio, at the pacing rate achieved with beta-blockade alone, increased from 5 to 27%. The author concluded that the absence of a further increase in coronary blood flow during atrial pacing, suggests that at that time the peripheral actions of nifedipine may be dominant. However, regional changes in coronary perfusion could also exert a beneficial effect.

Excellent clinical responses have been demonstrated by our group[27] when 6×10 mg $24\ h^{-1}$ nifedipine was added to the therapy of patients with unstable angina, who remained symptomatic with maximal beta-adrenergic blockade therapy, nitrates and bedrest. Forty-two out of 52 patients thus treated had no return of symptoms, none required further pain relief during the 48 h subsequent observation in the coronary care unit and none had further instability in their electrocardiogram. Since no significant systemic hemodynamic changes could be demonstrated after nifedipine in 18 patients studied, changes in coronary vasomotor tone were apparently responsible for this dramatic clinical improvement. These results have been obtained in a single blind study and await confirmation in further randomized double-blind studies.

Thus, combined therapy with beta-blockers and verapamil or nifedipine may be an important addition to the treatments of different forms of ischemic heart disease. No answers can at present be given to the questions as to which calcium antagonists (verapamil, nifedipine or eventually other slow channel blockers like diltiazem) might be most effective in combination with beta-blocking agents.

Table 1 summarizes the beneficial effects of combined beta-blocker/calcium antagonist treatment on exercise duration or pacing time to angina in some recently published studies.

Electrophysiologic effects of combined beta-blocker/calcium antagonist therapy

Both beta-blockers and calcium antagonists are able to modify sinus and atrioventricular nodal function. Beta-blocking agents slow sinus node discharge and increase sino-atrial conduction time, while sinus node recovery time is not significantly affected. Most importantly, abnormalities of sinus node function are accentuated by beta-blockade. Furthermore, these agents prolong atrioventricular conduction time and atrioventricular nodal refractoriness[28].

Despite similar basic mechanisms of action, the slow channel blocking agents verapamil and nifedipine have different clinical electrophysiologic effects[29]. When administered acutely (i.e. sublingual nifedipine or intravenous verapamil) heart rate is accelerated. Sinus nodal recovery and conduction times are unaltered. However, in patients with sinus node dysfunction, verapamil may prolong sinus node recovery time, eventually leading to sinus arrest.

Verapamil slows atrioventricular conduction time and increases atrioventricular refractoriness, while

Table 1 Exercise duration (min; symptom limited) or pacing time to angina in patients with combined therapy, when compared to placebo and/or monotherapy with a calcium antagonist or a beta-blocker

		Beta-blockade + verapamil		
	Placebo	Propranolol	Verapamil	Propranolol + verapamil
Subramanian *et al.*[7] (modified Bruce protocol)	4·8	6·8	8·0	10·1
Leon *et al.*[8] (Redwood protocol; 20 W every 3 min)	5·1	6·4	8·5	9·8
		Beta-blockade + nifedipine		
	Placebo	Propranolol	Nifedipine	Propranolol + nifedipine
Bassan *et al.*[14] (Redwood protocol; 20 W every 3 min)	not given	4·2	not given	6·2
Tweddel *et al.*[17] (50 W for 3 min; then 50 W increments every min)	4·35	4·8	not given	5·1
Daly *et al.*[15] (pacing time to angina)		4·75*		7·0
	Placebo	Atenolol	Nifedipine	Atenolol + nifedipine
Broustet *et al.*[16] (30 W every 3 min)	9·2	11·5	not given	12·3

*Some patients in this study received other beta-blockers.

nifedipine clearly has opposite effects on atrioventricular function. The effects of verapamil and nifedipine are the result of a complex interplay between their direct action on the sinus and atrioventricular node on one hand and the changes induced by their stimulation of the sympathetic nervous system on the other. The latter reflex mechanism, provoked by the decrease in peripheral vascular resistance, may be attenuated when both drugs are administered less acutely. This may explain the decrease in heart rate after oral verapamil administration[30,31] in some studies and the lack of an increase in heart rate with chronic nifedipine therapy[11–13]. Furthermore, when sympathetic reflex mechanisms are blocked, the direct electrophysiologic actions of calciumantagonists may become more apparent and important.

VERAPAMIL AND BETA-BLOCKADE

Different studies have described case reports of patients on beta-blockade, who developed sinus arrests, severe atrioventricular conduction disturbances and/or asystole after adding verapamil intravenously to their therapy[18–21]. Combined therapy in these patients has mainly been administered to treat supraventricular tachycardias. These adverse experiences have made many physicians reluctant to use this drug combination. However, the electrophysiologic and hemodynamic effects of combined slow channel and beta-blockade might produce less adverse reactions in patients in sinus rhythm.

The electrophysiologic effects of verapamil, when administered intravenously in patients in sinus rhythm and receiving oral propranolol treatment (mean dose 234 mg day^{-1}; range 40 to 1280 mg day^{-1}) have recently been studied by Winniford *et al.*[32]. A dose of 0·15 mg kg^{-1} verapamil was followed by a slight decrease in heart rate, while the A-H interval increased by 19% and the H-V interval remained unchanged (Fig. 2).

In their study, though in a limited number of patients, Seabra-Gomes *et al.*[33] demonstrated that combined verapamil and beta-blocking therapy can have additive effects on atrioventricular conduction. At a constant paced heart rate, intravenous

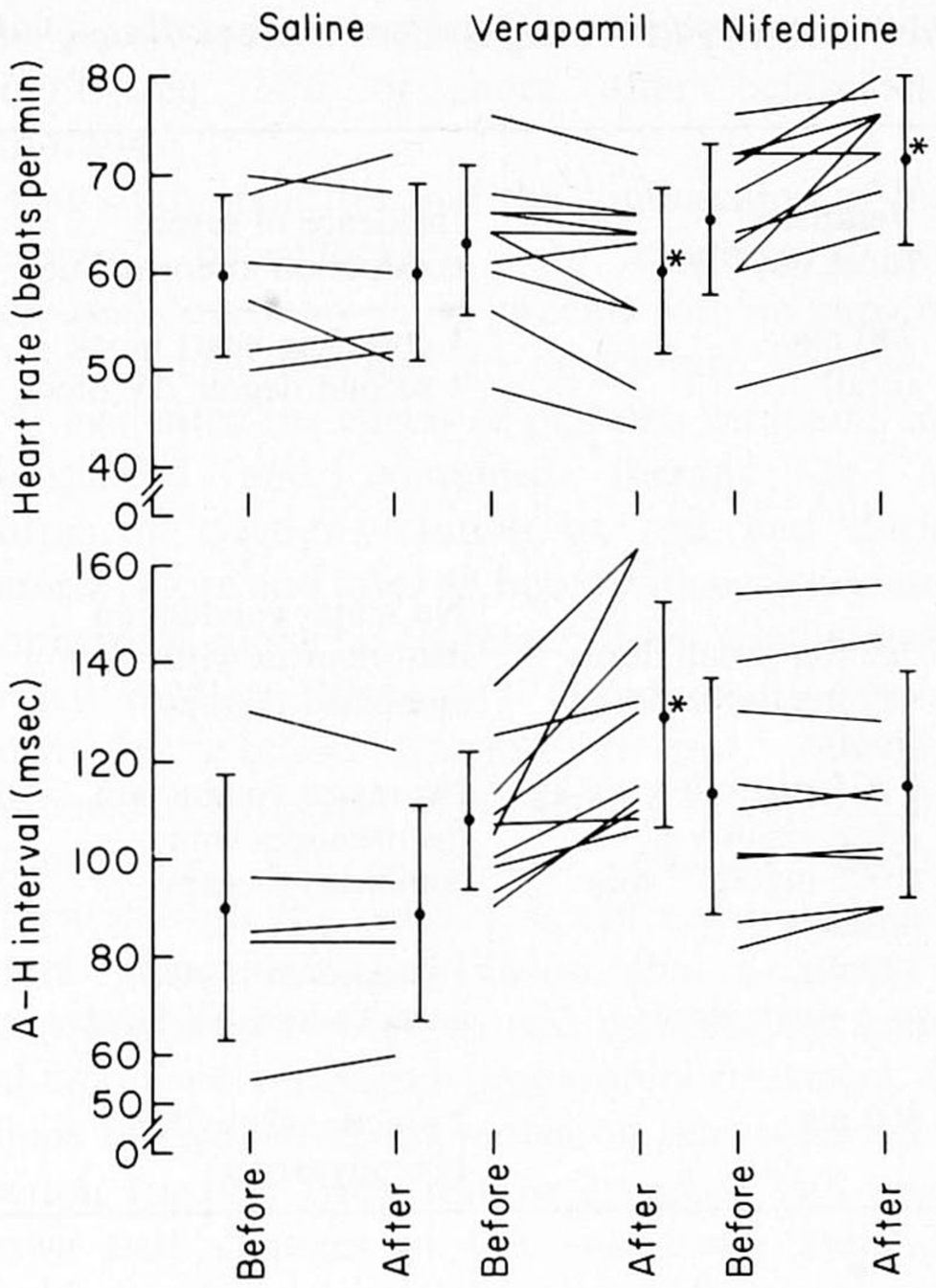

Figure 2 Heart rate and A-H interval, before and after the administration of saline, verapamil or nifedipine to beta-blocked patients. The heart rate was reduced by verapamil and increased by nifedipine. The A-H interval was lengthened only by verapamil. Asterisks indicate $P < 0{\cdot}05$ in comparison to the same pharmacologic agent before drug administration (Winniford *et al.*[32]). Reproduced with permission.

administration of verapamil, 0·1 mg kg^{-1}, after intravenous administration of practolol, 0·1 mg kg^{-1}, caused prolongation of the P-R interval, while no significant prolongation was observed with each drug alone.

Two studies recently have stressed that the changes in atrioventricular conduction seen with combined therapy, might be mainly caused by verapamil. Packer *et al.*[34] administered increasing oral doses of verapamil, up to 120 mg, to coronary artery disease patients already receiving high doses of propranolol or metoprolol. Even small doses of verapamil (40 mg) decreased heart rate in these highly beta-blocked patients. Furthermore, the P-R interval increased slightly when the 120 mg dose of oral verapamil was added to the chronic beta-blocker therapy. However, in the same patients, more than 24 h after withdrawal of propranolol or metoprolol, and after a dose of 120 mg verapamil, similar increases in P-R interval were still present. Importantly, one patient developed a junctional rhythm, once after verapamil during high dose propranolol treatment and once after verapamil administration 6 h after discontinuation of propranolol. This junctional rhythm did not recur 24 h after propranolol withdrawal, when the same dose of verapamil was given.

Leon *et al.*[8] compared the effectiveness of high and low doses of verapamil, and combined therapy of verapamil and propranolol in patients with chronic angina pectoris. Combination of propranolol and verapamil (407 mg ± 25 mg day^{-1}) caused a greater decrease in heart rate than verapamil alone. On the other hand, as well low (320 mg) as high (480 mg day^{-1}) doses of verapamil induced similar changes in P-R interval as combined therapy. The latter two reports both demonstrate a slight decrease in heart rate with combined therapy when compared with 'mono' therapy. Furthermore, they may indicate that atrioventricular conduction changes are mainly caused by verapamil.

The incidence of severe conduction disturbances in five recent reports are represented in Table 2. One could conclude that approximately 5% of patients develop important adverse reactions. Two important comments must be made: first, from these data one cannot judge the long-term effect of prolonged combined verapamil/beta-blocker treatment; secondly, most of the patients included where on beta-blocker therapy before combination therapy was started and this condition might have selected a patient population with better cardiac conduction characteristics than average.

NIFEDIPINE AND BETA-BLOCKADE

Most studies have demonstrated that adding beta-blockade to nifedipine treatment, results in lowering the heart rate. Thus, the frequently observed increase in heart rate observed on monotherapy with nifedipine, caused by its reflex sympathetic stimulation, can be counterbalanced by beta-blockade. This is of particular importance, since an increase in anginal complaints can sometimes be encountered, apparently due to mild sinus tachycardia, in patients on nifedipine therapy alone[31].

In patients on chronic beta-blockade, nifedipine does not or only slightly influence heart rate[11,13–15,32,35]. At present, to our knowledge, no detrimental effects of combined nifedipine/beta-

Table 2 Incidence of severe conduction disturbances in five recent reports in patients on combined verapamil/beta-blocker treatment

Authors	No. of patients (*n*)	Beta-blocker +dose	Verapamil (dose day^{-1})	Incidence of severe conduction abnormalities
Lessem *et al.*[9]	32	*n*=20 Propranolol 240 mg *n*= 5 Atenolol 100 mg *n*= 4 Pindolol 15 mg *n*= 2 Metoprolol 150 mg *n*= 1 Sotalol 320 mg (oral)	240 mg (oral)	1 complete heart block 1 second degree AV block
Leon *et al.*[8]	11	Median dose: 240 mg Propranolol (range 160–320 mg) (oral)	320 mg (small dose) 480 mg (large dose) (oral)	No major conduction disturbances with combined therapy
Kieval *et al.*[36]	20	Median dose: 160 mg Propranolol (range 40–480 mg) (oral)	0·025 mg to 0·1 mg kg^{-1} intravenously + 0·005 mg kg^{-1} min^{-1} infusion	No major conduction disturbances with combined therapy
Packer *et al.*[34]	15	*n*=13 Propranolol: mean dose 502 mg (range 160–1280 mg) *n*= 2 Metoprolol: 400 mg	120 mg as a single dose	1 junctional rhythm no advanced AV block
Subramanian *et al.*[7]	54	Propranolol 60–120 mg daily	360 mg	2 junctional rhythm 1 'bradycardia'

blocker therapy on atrioventricular nodal function have been reported

Winniford *et al.* could not demonstrate changes in A-H or H-V intervals when nifedipine was added to chronic propranolol therapy[32] (Fig. 2). Thus, contrary to verapamil, in the clinical situation, nifedipine does not further prolong atrioventricular conduction in beta-blocked patients.

Hemodynamic effects of combined beta-blocker/calcium antagonist therapy

VERAPAMIL + BETA-BLOCKADE

Seabra-Gomes[33] compared the effect of administration of intravenous practolol, verapamil and a combination of the two drugs, all at 0·1 mg kg^{-1} in patients with coronary artery disease. After heart rate had been controlled by atrial pacing, administration of verapamil intravenously after practolol, resulted in a decrease in LV dP/dt_{max} and cardiac index. Practolol alone did not influence hemodynamics when bradycardia was abolished by pacing, however verapamil alone caused a reduction in dP/dt_{max}. This author therefore emphasized caution with the combination of these drugs in patients with an impaired myocardial function. In patients with supraventricular tachycardia, pronounced hypotension has been seen after verapamil has been administered intravenously in patients on chronic beta-blockade[18]. However, hemodynamic changes might be less obvious with combination therapy when not given during an acute phase of supraventricular tachycardia and when administered orally.

Several recent reports have re-evaluated combined administration of verapamil and propranolol or metoprolol. Packer *et al.*[34] described the hemodynamic effects of oral administration of different doses of verapamil in 15 patients with severe angina pectoris, who had been treated with high doses of propranolol (mean 502 mg day^{-1}) or metoprolol (400 mg day^{-1}). At doses of 40 and 80 mg, systemic vascular resistance, stroke volume index and mean pulmonary capillary wedge showed no significant changes. When 120 mg verapamil was given during beta-blockade, significant decreases in mean arterial pressure, cardiac index (−0·38 liters min^{-1} m^{-2}) and heart rate were accompanied by a significant decline in stroke volume index and increases in pulmonary capillary wedge pressure.

Two patients developed hypotension during administration of the beta-blocker and 120 mg verapamil, but neither was symptomatic. Verapamil did not produce decreases in cardiac index or heart rate and only minimal changes in pulmonary

capillary wedge and mean right atrial pressure when administered 24 h or more after beta-blocker withdrawal.

This study indicates that the combination of high doses of beta-blockers with commonly used verapamil doses may cause patients with an impaired left ventricular function to deteriorate. Bonow *et al.*[30] evaluated the effects of placebo, verapamil and propranolol and combined therapy on left ventricular ejection fraction at rest and during exercise before and after 48 hours with each regimen. Propranolol alone at different doses (individually titrated; median 240 mg day^{-1}) did not modify left ventricular ejection fraction at rest. Although combined treatment with 480 mg verapamil/day reduced the left ventricular ejection fraction compared with the control, it did not significantly reduce ejection fraction below that attained by verapamil alone, except, in two patients. Verapamil and combined verapamil–propranolol treatment did reduce the magnitude of reduction that occurred in ejection fraction from rest to exercise. This study shows that changes in left ventricular function, observed after verapamil treatment, do not become more apparent when moderate beta-blockade is concomitantly given. However, it is obvious that in individual patients left ventricular function can become impaired. In fact, two patients experienced exertional dyspnea during combined therapy.

Kieval *et al.*[36] evaluated the hemodynamic effects of intravenous verapamil in 20 patients with chronic stable angina, who had been treated with an average dose of 160 mg propranolol, all with an ejection fraction greater than 40%. Patients received verapamil intravenously at a dose of 0·025, 0·05 or 0·1 mg kg^{-1} over a two minutes period followed by an infusion of 0·005 mg kg^{-1} min^{-1} for a maximum of 60 min. A substantial decrease of mean arterial pressure was accompanied by a significant reduction in systemic vascular resistance. Despite this unloading effect, concomitant increases in cardiac index, mean Vcf and ejection fraction were not observed. Interestingly, also max dP/dt remained unchanged. Kieval stated that the lack of improvement in the indices of left ventricular function suggests some interaction of the two drugs, which may be of concern in patients with evidence of depressed myocardial performance.

Few studies have shown an amelioration in cardiac performance in non-beta-blocked patients after verapamil alone, while others did not demonstrate similar changes[37–41]. Thus, one might argue that lack of improvement in the indices of left ventricular function, is mainly due to verapamil itself, and not to the additional low dose beta-blockade. All the previous studies indicate that, despite its vasodilating properties, verapamil does not improve cardiac performance (as can usually be seen with nifedipine), when added to beta-blockade treatment. Actually, when concomitantly given with high doses of beta-blockers, left ventricular function may importantly become impaired. For this reason, it must also be stressed that only patients with relatively well preserved left ventricular function were actually included. Since Chew *et al.* showed that verapamil alone can cause deterioration in patients with an impaired left ventricular function (ejection fraction below 30%, or pulmonary capillary wedge higher than 20 mmHg), one must warn against the use of combined beta-blocker/verapamil therapy in this subset of patients. The incidence of adverse hemodynamic reactions after combined therapy in different recent studies is summarized in Table 3.

NIFEDIPINE + BETA-BLOCKADE

Most authors agree that under resting conditions the negative intrinsic inotropic effect of nifedipine, seen in animal experiments and after direct intracoronary administration in humans[1], is not apparent when the drug is taken orally[42–46]. However, the negative intrinsic inotropic effect of nifedipine may become apparent if the patients receive beta-blockers concomitantly.

Case reports on adverse hemodynamic interactions between nifedipine and beta-blockade have indeed been published[22–26]. Cardiogenic shock or frank congestive heart failure occurred several days after adding nifedipine to the treatment of patients on chronic beta-blockade. Importantly, most patients involved had a history of recurrent myocardial infarction. Motté *et al.*[24] reported the development of electromechanical dissociation at the onset of an acute myocardial infarction, which occurred 2 h after administration of 20 mg nifedipine in a beta-blocked patient. The patient recovered, and his slow sinusal rhythm disappeared after catecholamine administration. Contrary to the incidental reports on adverse experiences after adding nifedipine to beta-blocked patients, the hemodynamic interaction between the two drugs seems to be beneficial rather than detrimental in controlled clinical reports.

Joshi[47], at a constant atrial paced rate,

Table 3 Incidence of adverse hemodynamic changes after combined verapamil/beta-blocker treatment

Authors	No. of patients (*n*)	Beta-blocker	Verapamil	Adverse experience
Lessem et al.[9]	32	Propranolol, 240 mg (20) Atenolol, 100 mg (5) Pindolol, 15 mg (4) Metoprolol, 150 mg (2) Sotalol, 320 mg (1)	240 mg	None
Bonow *et al.*[30]	11	Propranolol, 240 mg (range 160–320 mg)	480 mg	2 exertional dyspnea
Subramanian *et al.*[7]	54	Propranolol, 120 mg	360 mg	1 exertional dyspnea 3 cardiac failure 4 hypotension
Packer *et al.*[34]	15	Propranolol, mean 502 mg (range 160–128 mg (13) Metroprolol, 400 mg (2)	120 mg (single dose)	2 marked hypotension
Kieval *et al.*[36]	20	Propranolol, 160 mg (range 40–480 mg)	Verapamil iv 0·025 to 0·1 mg kg^{-1} +continuous infusion	None

administered 10 mg of nifedipine sublingually to 12 coronary artery disease patients who had already been treated with atenolol (400 mg day^{-1}). He observed a significant decrease of peak dP/dt and peak $(dP/dt)/P$ which suggested the negative inotropic effect of the drug was more evident after beta-blockade. Nifedipine also reduced systemic vascular resistance which was associated with decreases in systolic blood pressure and increases in left ventricular output, while left ventricular end-diastolic pressure was unchanged.

Koch[48] gave 10 mg nifedipine sublingually to patients with coronary artery disease pretreated with metoprolol. An increase of adrenaline and noradrenaline plasma levels was observed after nifedipine. Stroke volume increased, and the left ventricular filling pressure which had increased after metoprolol alone, was reduced.

Daly *et al.*[15] evaluated the effects of adding nifedipine to chronic propranolol therapy in patients with proven coronary artery disease. At rest, heart rate and cardiac output increased, while pulmonary artery diastolic pressure remained unchanged after adding nifedipine. During exercise, however, no increase in cardiac output was observed, while total peripheral resistance and arterial systolic pressure were lowered, as compared to the control period on propranolol alone. During exercise, when comparing the effect of acebutolol alone to combined therapy with nifedipine, Schmutzler *et al.*[49] also did not observe increases in cardiac output. However, peripheral arterial resistance and arterial systolic pressure were lowered, and this, combined with an unchanged heart rate, resulted in a decrease in the rate-pressure product. This indicates that at least in some patients with coronary artery disease, left ventricular work is further reduced after adding nifedipine to beta-blockade, which implies lower myocardial oxygen requirements at a given level of physical activity. The hemodynamic beneficial interaction was further demonstrated by slight decreases in left ventricular end-diastolic pressures and mean pulmonary artery pressure with combined therapy when compared to therapy with acebutolol alone.

Pfisterer *et al.*[35] performed hemodynamic and radionuclide ejection fraction measurements at rest and during exercise before any treatment in patients with stable CAD, 1 h after administration of nifedipine or acebutolol and again 1 h after combined therapy. At rest, ejection fraction was lower and cardiac index was unchanged with combined therapy when compared with the control data. However, the negative effects of acute beta-blockade alone on cardiac index, resting ejection fraction and total peripheral resistance were clearly counterbalanced by nifedipine. During exercise, at the same level as achieved without drugs, additive beneficial effects of both drugs on the pressure-rate product were observed. Combined therapy limited the amount of ejection fraction decrease, observed

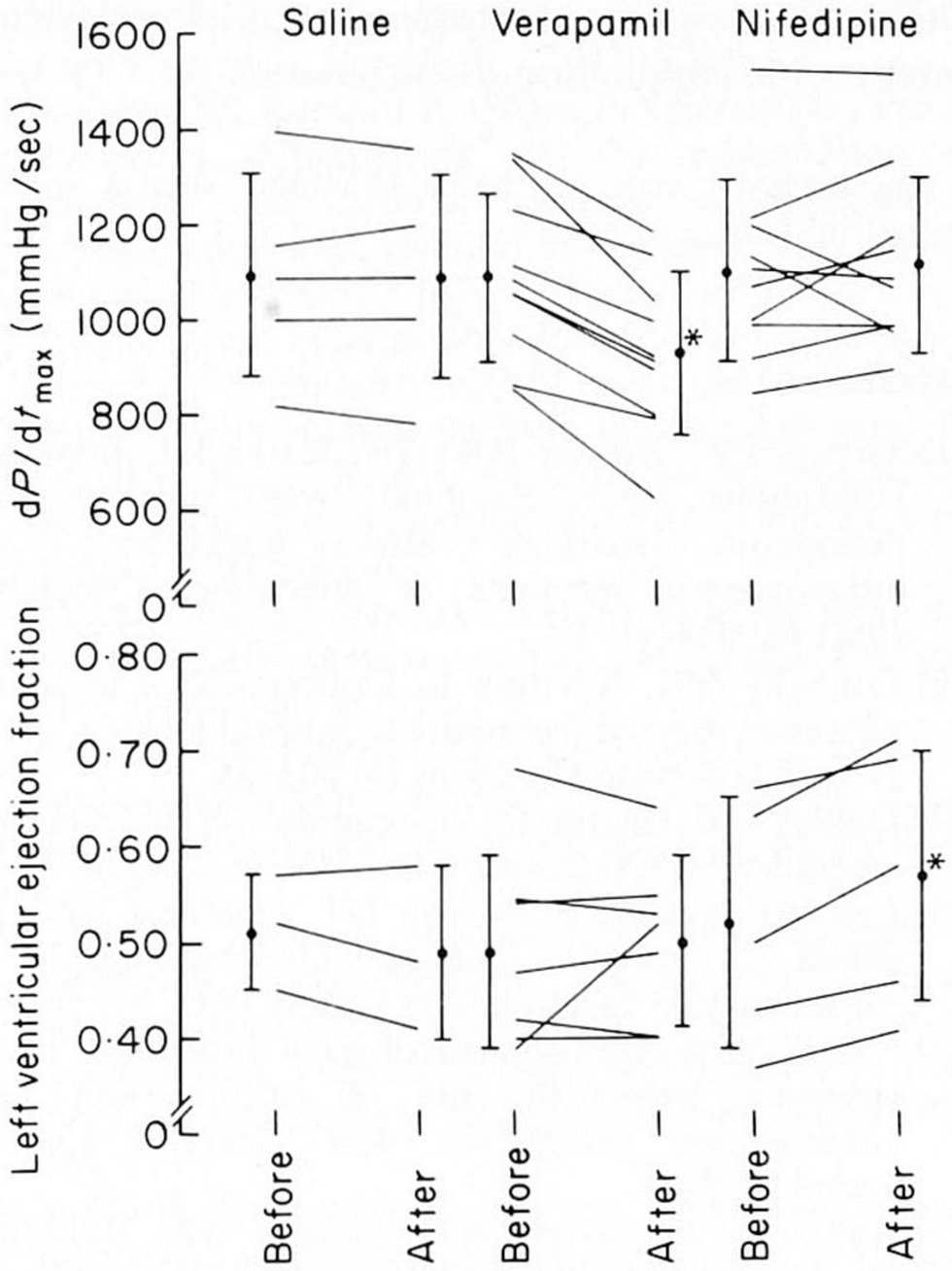

Figure 3 Left ventricular peak positive dP/dt and left ventricular ejection fraction, before and after the administration of saline solution, verapamil or nifedipine to beta-blocked patients. Left ventricular dP/dt was reduced by verapamil; ejection fraction increased after administration of nifedipine. Asterisks indicate $P < 0{\cdot}05$ in comparison with the same pharmacologic agent before drug administration (Winniford *et al.*[32]). Reproduced with permission.

during exercise, to a similar degree as single therapy. Interestingly, between a subgroup of patients with a cardiac index at rest of less than 2·6 liters $min^{-1} m^{-2}$, and the remaining patients, no differences were seen.

Winniford *et al.*[32] also observed an increase in cardiac output and ejection fraction, as measured by radionuclide ventriculography, after adding nifedipine to beta-blocked patients. Contrary to the results of Joshi[47], after adding nifedipine no changes in LV dP/dt were measured (Fig. 3).

The previous studies indicated that in patients with stable CAD the unwanted stimulation of the sympathetic nervous system after nifedipine administration can be blocked by beta-receptor antagonists. Thus the intrinsic negative inotropic effect of the drug may become more apparent after beta-blockade. Yet the vasodilatory effect of nifedipine appears to predominate and thus a combination of the drug appears attractive as at a lower heart rate and afterload, cardiac output is maintained.

In patients with unstable angina pectoris that were still symptomatic after maximal treatment with nitrates and beta-blockers, the hemodynamic effect of adding nifedipine (10 mg sublingually) has been studied by our group[27]. No major hemodynamic changes were observed after adding nifedipine to the treatment while the drug proved to be highly effective in relieving anginal complaints. This suggests that the known peripheral hemodynamic effects of the drug are not the major cause in relieving angina pectoris in this group of patients. Rather the effectiveness of the drug appears to be related to its capacity to counteract the increased vasomotor tone of the coronary arteries, which is the main disturbance in unstable angina.

Summary

For more than two decades nitrates and beta-blocking agents have been the mainstay in the medical treatment of chronic stable angina pectoris. While this treatment has given symptomatic relief in an important number of patients, there is a great need for further development of potent anti-anginal and anti-ischemic agents. The calcium antagonists are increasingly accepted as the "third" weapon against ischemic heart disease. These drugs with powerful peripheral and coronary vasodilating properties are drugs of choice in vasospastic angina and can be effective as monotherapy for chronic stable angina pectoris[31,50–53]. Their combination with beta-blocking agents seems attractive since both classes of drugs have different modes of action. The effectiveness of beta-blocking agents is primarily attributed to a decrease in myocardial oxygen requirements as reflected by a reduction in heart rate, contractility and blood pressure. While calcium antagonists can further reduce cardiac work and thus myocardial oxygen requirements by decreasing peripheral vascular resistance, they also vasodilate coronary arteries and can thus counterbalance the reduction in coronary blood flow, generally observed with beta-blocking therapy. Furthermore, they improve myocardial diastolic function and may, as is the case with beta-blockers, have cardioprotective action at the subcellular level.

The unwanted increase in heart rate, due to reflex

stimulation of the sympathetic nervous system after slow channel calcium blockade, is abolished when beta-blockers are concomitantly given.

Thus, their differing and perhaps complementary actions would make it seem advisable to begin with a combination of these drugs in the clinical treatment of ischemic states of the myocardium. Indeed, their beneficial interaction has been demonstrated in different well controlled recent studies. Exercise capacity in patients with stable angina pectoris is consistently improved, while adding nifedipine to unstable beta-blocked angina pectoris patients can cause dramatic symptomatic relief.

On the other hand, both classes of drugs have direct negative inotropic properties, and, in patients with an impaired left ventricular function, a synergistic detrimental effect on contractility might be feared. Indeed, case reports have been published on this adverse interaction and have made some physicians reluctant to use this drug combination. Furthermore, combination of verapamil and beta-blockade has incidentally resulted in severe conduction disturbances, due to a synergistic negative effect on sinus node function and atrio-ventricular conduction. We reviewed the hemodynamic and electrophysiologic interactions of beta-blockers and calcium antagonists. A 5 to 10% incidence of important adverse interactions with combined verapamil/beta-blockade therapy can be observed, while on the other hand an additive anti-anginal effect is obvious. Particularly in patients on high dose beta-blockade, a decrease in cardiac performance might become apparent. Negative additive chronotropic effects with combined nifedipine/beta-blocker therapy have not been reported and apart from occasionally observed temporary hypotension, adverse hemodynamic interactions are incidental. It must be stressed, however, that combination therapy has not been yet adequately evaluated in patients with severely impaired left ventricular function.

We conclude that combination therapy can provide greater improvement in patients with stable coronary artery disease than monotherapy with either beta-blockade or slow channel calcium blockade alone. Furthermore, this combination appears to be safe and well tolerated in the great majority of patients with a well preserved or only moderately impaired left ventricular function. We caution against the routine use of combined therapy, especially when verapamil is involved in patients with more pronounced impairment of left ventricular function (or conduction disturbances).

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References

(1) Serruys PW, Brower RW, Ten Katen HJ, Bom AH, Hugenholtz PG. Regional wall motion from radiopaque markers after intravenous and intracoronary injections of nifedipine. Circulation 1981; 63: 584–91.
(2) Connolly ME, Kersting F, Dollery CT. The clinical pharmacology of beta-adrenoceptor blocking drugs. Progr Cardiovasc Dis 1976; 19: 203–34.
(3) Dollery CT, George C. Propranolol—Ten years from introduction. Cardiovasc Clin 1974; 6: 255–65.
(4) Low RI, Takeda P, Mason DT, DeMaria AN. The effects of calcium channel blocking agents on cardiovascular function. Am J Card 1982; 49: 547–53.
(5) Nayler WG. The pharmacological protection of the ischaemic heart: the use of calcium and beta-adrenoceptor antagonists. Eur Heart J 1980; 1 (suppl B): 5–13.
(6) Robertson RS, Wood AJJ, Vaughn WK, Robertson D. Exacerbation of vasotonic angina pectoris by propranolol. Circulation 1982; 65: 281–5.
(7) Subramanian BV, Bowles MJ, Davies AB, Raftery EB. Combined therapy with verapamil and propranolol in chronic stable angina. Am J Card 1982; 49: 125–32.
(8) Leon MB, Rosing DR, Bonow RO, Lipson LC, Epstein SE. Clinical efficacy of verapamil alone and combined with propranolol in treating patients with chronic stable angina pectoris. Am J Card 1981; 48: 131–9.
(9) Lessem J. Combined administration of verapamil and beta-blockers in patients with angina pectoris. In: Zanchetti A, Krikler DM, eds. Calcium antagonism in cardiovascular therapy. Amsterdam: Excerpta Medica, 1981: 159–66.
(10) Fox K, Jonathan A, Selwyn A. Combined high-dosage administration of nifedipine and propranolol in patients with angina pectoris. In: Puech P, Krebs R, eds. Fourth International Adalat Symposium. Amsterdam/Oxford/Princeton: Excerpta Medica, 1980: 147–53.
(11) Dargie HJ, Lynch PG, Krikler DM, Harris L, Krikler S. Nifedipine and propranolol: a beneficial drug interaction. Am J Card 1981; 71: 676–82.
(12) Lynch P, Dargie H, Krikler S, Krikler D. Objective assessment of antianginal treatment: a double-blind comparison of propranolol, nifedipine, and their combination. Br Med J 1980; 281: 184–7.
(13) Kenmure ACF, Scruton JH. A double-blind controlled trial of the antianginal efficacy of nifedipine compared with propranolol. Br J Clin Pract 1980; 34: 149–51.
(14) Bassan M, Weiler-Ravell D, Shalev O. The additive antianginal action of oral nifedipine in patients receiving propranolol. Circulation 1982; 66: 710–6.
(15) Daly K, Bergman G, Rothman M, Atkinson L, Jackson G, Jewitt DE. Beneficial effect of adding

nifedipine to beta-adrenergic blocking therapy in angina pectoris. Eur Heart J 1982; 3: 42–6.
(16) Broustet JP, Rumeau P, Guern P, Cherrier JF, Pic A, Bonnet J. Comparison of the combination of nifedipine and atenolol with the combination of nitroglycerine and atenolol in patients with angina pectoris. Eur Heart J 1980; 1 (suppl B): 59–64.
(17) Tweddel AC, Beattie JM, Lawrie TDV, Hutton I. Effects of nifedipine on physical performance in patients with angina pectoris on beta-blockers. In: Puech P, Krebs R, eds. Fourth International Adalat Symposium. Amsterdam/Oxford/Princeton: Excerpta Medica, 1980: 143–6.
(18) Krikler DM, Spurell RAJ. Verapamil in the treatment of paroxysmal supraventricular tachycardia. Postgrad Med J 1974; 50: 447–53.
(19) Boothby CB, Garrard CS, Pickering D. Verapamil in cardiac arrhythmias. Br Med J 1972; 2: 348–9.
(20) Benaim ME. Asystole after verapamil. Br Med J 1972; 2: 169–70.
(21) Denis B, Pellet J, Machecourt J, Martin-Noël P. Vérapamil et bêta-bloquant. Une association thérapeutique dangereuse. Nouv Presse Med 1977; 6: 2075.
(22) Robson RH, Vishwanath MC. Nifedipine and beta-blockade as a cause of cardiac failure. Br Med J 1982; 284: 104.
(23) Staffurth JS, Emery P. Adverse interaction between nifedipine and beta-blockade. Br Med J 1981; 282: 225.
(24) Motté G, Chanu B, Sébag C, Bénaim P. Nifédipine et bêta-bloqueur: une association potentiellement dangereuse? Nouv Presse Med 1980; 9: 379–80.
(25) Anastassiades CJ. Nifedipine and beta-blocking drugs. Br Med J 1980; 281: 1251–2.
(26) Opie LH, White DA. Adverse interaction between nifedipine and beta-blockade. Br Med J 1980; 281: 1462.
(27) Serruys PW, Steward R, Booman F, Michels R, Reiber JHC, Hugenholtz PG. Can unstable angina pectoris be due to increased coronary vasomotor tone? Eur Heart J 1980; 1 (suppl B): 71–85.
(28) Wellens HJJ. Electro-physiological effects of beta-blocking agents as studied by programmed stimulation of the heart. In: Poppers PJ, Van Dijk B, Van Elzakker AHM, eds. Beta-blockade and anesthesia. Astra Pharmaceutica, 1980: 65–70.
(29) Mitchell LB, Schroeder JS, Mason JW. Comparative clinical electrophysiologic effects of diltiazem, verapamil and nifedipine: a review. Am J Card 1982; 49: 629–35.
(30) Bonow RO, Leon MB, Rosing DR, Kent KM, Lipson LC, Bacharach SL, Green MV, Epstein SE. Effects of verapamil and propranolol on left ventricular systolic function and diastolic filling in patients with coronary artery disease: radionuclide angiographic studies at rest and during exercise. Circulation 1982; 65: 1337–50.
(31) Subramanian VB, Bowles MJ, Khurmi NS, Davies AB, Raftery EB. Randomized double-blind comparison of verapamil and nifedipine in chronic stable angina. Am J Cardiol 1982; 50: 696–703.
(32) Winniford MD, Markham RV, Firth BG, Nicod P, Hillis LD. Hemodynamic and electrophysiologic effects of verapamil and nifedipine in patients on propranolol. Am J Cardiol 1982; 50: 704–10.
(33) Seabra-Gomes R, Rickards A, Sutton R. Hemodynamic effects of verapamil and practolol in man. Eur J Cardiol 1976; 4/1: 79–85.
(34) Packer M, Meller J, Medina N, Yushak M, Smith H, Holt J, Guererro J, Todd GD, McAllister RG, Gorlin R. Hemodynamic consequences of combined beta-adrenergic and slow calcium channel blockade in man. Circulation 1982; 65: 660–8.
(35) Pfisterer M, Müller-Brand J, Burkart F. Combined acebutolol/nifedipine therapy in patients with chronic coronary artery disease: additional improvement of ischemia-induced ventricular dysfunction. Am J Cardiol 1982; 49: 1259–66.
(36) Kieval J, Kirsten EB, Kessler KM, Mallon SM, Myerburg RJ. The effects of intravenous verapamil on hemodynamic status of patients with coronary artery disease receiving propranolol. Circulation 1982; 65: 653–9.
(37) Ferlinz J, Easthope JL, Aronow WS. Effects of verapamil on myocardial performance in coronary disease. Circulation 1979; 59: 313–9.
(38) Chew CYC, Hecht HS, Collett JT, McAllister RG, Singh BN. Influence of severity of ventricular dysfunction on hemodynamic responses to intravenously administered verapamil in ischemic heart disease. Circulation 1981; 47: 917–23.
(39) Singh BN, Roche AHG. Effects of intravenous verapamil on hemodynamics in patients with heart disease. Am Heart J 1977; 94: 593–9.
(40) Ryden L, Saetre H. The hemodynamic effect of verapamil. Eur J Clin Pharmacol 1971; 3: 153–7.
(41) Atterhog JH, Ekelund LG. Hemodynamic effects of intravenous verapamil at rest and during exercise in subjectively healthy middle-age men. Eur J Clin Pharmacol 1978; 8: 317–22.
(42) Stone PH, Antman EM, Muller JE, Braunwald E. Calcium channel blocking agents in the treatment of cardiovascular disorders. Part II: hemodynamic effects and clinical application. Ann Intern Med 1980; 93: 886–904.
(43) Lydtin H, Lohmoller G, Lohmoller R, Schmitz H, Walter I. Hemodynamic studies on adalat in healthy volunteers and in patients. In: Lochner W, Braasch W, Kronenberg G, eds. Proceedings of the 2nd International Adalat Symposium. Berlin/Heidelberg/New York: Springer Verlag, 1975: 112.
(44) Van den Brand M, Remme WJ, Meester GT, Tiggelaar-de Widt, Ruiter de R, Hugenholtz PG. Hemodynamic effect of nifedipine in patients catheterized for coronary artery disease. In: Lochner W, Braasch W, Kroneberg G, eds. Proceedings of the 2nd International Adalat Symposium. Berlin/Heidelberg/New York: Springer Verlag, 1975: 146.
(45) Kober G, Becker HJ, Kaltenbach M. Left ventricular hemodynamics in patients at rest before and after nifedipine. In: Lochner W, Braasch W, Kroneberg G, eds. Proceedings of the 2nd International Adalat Symposium. Berlin/Heidelberg/New York: Springer Verlag, 1975: 164.
(46) Piegas LS, Neto FP, Konstadinidis T, de Magalhaes

HM, de Souza EMR, Jatene AD. Hemodynamic evaluation of a new antianginal drug: nifedipine. In: Jatene AD, Lichtlen PR, eds. Proceedings of the 3rd International Adalat Symposium. Amsterdam/Oxford: Excerpta Medica, 1976: 76.

(47) Joshi PI, Dalal JJ, Ruttley MSJ, Sheridan DJ, Henderson AH. Nifedipine and left ventricular function in beta-blocked patients. Br Heart J 1981; 45: 457–9.

(48) Koch G. Beta-receptor and calcium blockade in ischemic heart disease: effects on systemic and pulmonary hemodynamics and on plasma catecholamines at rest and during exercise. In: Puech P, Krebs R, eds. Fourth International Adalat Symposium. Amsterdam/Oxford/Princeton: Excerpta Medica, 1980: 131–42.

(49) Schmutzler H, Dorow P, Krais T, Rutsch W. Central hemodynamics under conditions of rest and load in patients with coronary artery disease treated with a combination of a beta-blocker and nifedipine. In: Puech P, Krebs R, eds. Fourth International Adalat Symposium. Amsterdam/Oxford/Princeton: Excerpta Medica, 1980: 176–83.

(50) Winniford MD, Johnson SM, Mauritson DR, Rellas JS, Redish GA, Willerson JT, Hillis LD. Verapamil therapy for Prinzmetal's variant angina: comparison with placebo and nifedipine. Am J Cardiol 1982; 50: 913–8.

(51) Antman E, Muller J, Goldberg S, McAlpin R, Rubenfire M, Tabatznik B, Liang C, Heupler F, Achuff S, Reichek N, Geltman E, Kerin NZ, Neff RK, Braunwald E. Nifedipine therapy for coronary artery spasm. N Engl J Med 1980; 302: 1269–73.

(52) Brodsky SJ, Cutler SS, Weiner DA, McCabe CH, Ryan TJ, Klein MD. Treatment of stable angina of effort with verapamil: a double-blind, placebo-controlled randomized crossover study. Circulation 1982; 66: 569–74.

(53) Mueller HS, Chahine RA. Interim report of multicenter double-blind, placebo-controlled studies of nifedipine in chronic stable angina. Am J Med 1981; 71: 645–57.